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Hepatocyte iron accumulation: A new string to ribavirin's antiviral bow?

To the Editor:

Building on previous work, the recent article by Fillebeen and Pantopoulos elegantly demonstrates a role for iron as an inhibitor of hepatitis C virus (HCV) replication [1]. Using HCV-infected Huh7.5.1 hepatoma cells, the authors show a dose-dependent reduction in the expression of HCV viral proteins and RNA upon exogenous administration of iron. Moreover, the anti-viral effect of iron was attributed to the direct inhibition of the HCV RNA polymerase NS5B by iron [2].

However, the findings outlined in this article appear contrary to the prevailing perception of the role of iron in HCV infection. Disordered iron homeostasis is a frequent finding in HCV patients, and may be associated with adverse clinical outcomes [3]. An increased propensity to hepatic decompensation, an increased incidence of hepatocellular carcinoma, and a reduced response to treatment have all been reported in association with excess serum or hepatic iron [4–6]. The authors acknowledge these issues, and conclude by doubting whether iron-mediated inhibition of HCV replication would represent a realistic therapeutic target. These sentiments were echoed in the accompanying editorial [7].

The nucleoside analogue ribavirin forms a key component of the current standard of care for HCV treatment, in combination with pegylated interferon alpha. Despite its importance in augmenting treatment response and preventing relapse, its antiviral mechanism of action remains elusive [8]. Curiously, significant hepatic iron accumulation has been reported in HCV patients receiving ribavirin monotherapy for greater than 6 months [9,10]. These findings were attributed to the well-documented, dose-dependent haemolysis caused by ribavirin. However, excess iron accumulated predominantly in hepatocytes, rather than in phagocytic Kupffer cells, as might be expected following intravascular haemolysis [10]. Although hepatic iron accumulation during treatment was not associated with changes in liver transaminases, it is unclear whether treatment response was altered [10].

Iron accumulation in chronic HCV infection appears harmful. Given the findings by Fillebeen et al., it would be difficult to discount a potential role for iron in hepatocyte HCV eradication, which may be transiently facilitated by ribavirin therapy. At the very least, this potential mechanism of ribavirin action merits further investigation.

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Conflict of interest

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Reply to: Hepatocyte iron accumulation: A new string to ribavirin's antiviral bow?

This is a reply to the letter to the Editor by Ryan and Crowe:
We thank Drs. J.D. Ryan and J. Crowe for their comments to our recent article [1]. In their letter, they discuss earlier reports showing that prolonged treatment of HCV-infected patients with ribavirin associates with hepatic iron deposition, mainly in hepatocytes [2,3]. This is largely attributed to *extra*vascular hemolysis, a known side effect of ribavirin ([2] and references therein) even though one would expect a predominant distribution of excess iron within Kupffer cells. The authors further hypothesise that accumulation of iron within hepatocytes may potentiate the antiviral efficacy of this therapeutic regimen, considering that iron inhibits the replication of HCV in permissive Huh7.5.1 cells [1].

We completely agree that this hypothesis merits further exploration. It will be interesting to examine the effects of ribavirin in the infectious HCV replicon model, with or without exogenous iron administration. Nevertheless, given the complexity of the pharmacological responses to ribavirin *in vivo*, which impinges on systemic iron traffic, we should be cautious in extrapolating data from this cell culture model. Moreover, the iron deposition in hepatocytes of patients did not appear to affect the "biochemical or histologic response to ribavirin therapy" over a period of 9 months, even though sustained virological response (SVR) was not assessed [2]. A more recent prospective study evaluated how iron perturbations affect combination therapy with pegylated interferon and ribavirin [4]. The data revealed a negative correlation between iron load in Kupffer cells and the prospect of achieving SVR, and did not provide any evidence for potential benefits of hepatocyte iron accumulation. Further clinical studies with HCV-infected patients and, possibly, also experiments with humanized mouse models for HCV infection [5], may provide a more clear view on how hepatocyte iron accumulation interferes with antiviral therapy.

Conflict of interest

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